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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/226,895	01/07/1999	MICHAEL ROSENBLUM	D6205	8983

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 04/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/226,895	ROSENBLUM ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1,5-9 and 11-15 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1, 5-9, 11-15 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 22, 2005 has been entered.

2. Claim 1 has been amended. Claims 12-15 have been added. Claims 1, 5-9 and 11-15 are pending and under consideration.

3. The text of Title 35, U.S. Code not found in this action, can be found in a prior action.

4. Claims 1, 5-9 and 11-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

Claim 1 has been amended to incorporate the subject matter of drug-resistant leukemias as a pathophysiological state of an individual. The disclosure as filed does not support this amendment. The specification states on page 10, line 20 to page 11, line 2, (and original claim 4) that representative pathophysiological states which may be treated using the methods of the invention include retinoic acid receptor alpha selective acute myeloid leukemia, acute promyelocytic leukemia, lymphomas and myelomas. One of skill in the art would reasonable conclude that applicant was not in possession of the claimed invention with regard to the pathophysiological state of drug resistant leukemias at the time the specification was filed.

5. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear how claim 7 further modifies claim 1. Claim 1 requires that the immunotoxin is directed against the up-regulated CD38 antigen. Claim 7 states that the immunotoxin specifically targets cells expressing the CD38 antigen. The scope of claim 7 is the same as the scope of claim 1 because an immunotoxin directed against the up-regulated CD38 antigen would be the same as an immunotoxin which specifically targets the CD38 antigen.

6. Claims 1, 5, 7, 8 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Flavell et al (Cancer Research, 1997, Vol. 57, pp. 4824-4829, cited in a previous Office action) in view of Schlom ('Monoclonal AntibodiesThey'reMore and Less Than You Think', In: Molecular Foundations of Oncology, 1993, S. Broder, Ed, pp. 95-134).

Claim 1 is drawn in part to a method of treating an individual having lymphoma comprising administering to said individual a pharmacologically effective dose of a retinoid which up-regulates the expression of CD38 antigen and administering to said individual a pharmacologically effective dose of an immunotoxin directed against the up-regulated CD38 antigen. Claim 5 embodies the method of claim 1 wherein the retinoid is selected from a group comprising ATRA. Claim 7 embodies the method of claim 1 wherein said immunotoxin specifically targets cells expressing the CD38 antigen. Claim 8 embodies the method of claim 7 wherein said immunotoxin comprises a monoclonal antibody directed against the CD38 antigen conjugated to a toxin molecule. Claim 14 embodies the method of claim 1 wherein the pathophysiological state is lymphoma.

Flavell et al teach that the ability of immunotoxins to kill tumor cells is limited by heterogeneous expression of the target antigen on said tumor cells (Introduction, first paragraph). Flavell et al teach that this problem can be overcome by targeting three separate antigens on the tumor cells: CD38, CD19 and CD22, wherein said three monoclonal antibodies are conjugated to saporin. Flavell et al teach that when the immunotoxin CD38-saporin was used as a single agent it had some effectiveness, but that the individual immunotoxin was more effective when combined with the antiCD19 and antuCD22 immunotoxins due to the lack of adequate CD38 expression on all the tumor cells (page 4826, second column, under "Survival", lines 11-13). Flavell et al do not teach the administration of the antiCD38 immunotoxin in combination with a retinoid.

Schlom teaches that it is well known in the art that virtually any component of a tumor cell is susceptible to modulation. Schlom teaches that the practice of receptor modulation to increase the level of extracellular receptors targeted by monoclonal antibodies (pages 109-110 under the heading of "Up Regulation of Target Antigens") is recognized in the art (page 109-110, under the heading "Up Regulation of Target Antigens").

The abstract of Zhao et al (Blood, 1994, Vol. 84, No. 10, suppl 1, page 54A) teaches that liposomal ATRA up-regulated CD38 on lymphoma samples.

It would have been prima facie obvious at the time the claimed invention was made to administer liposomal ATRA in conjunction with the method of treatment of Flavell et al, or to administer liposomal ATRA with a CD38 immunotoxin alone, in order to treat lymphoma in a patient. One of skill in the art would have been motivated to do so by the teachings of Schlom on the well known principle of receptor modulation to increase the level of a target receptor on the cell surface, and the specific teachings of the abstract of Zhao et al on increasing CD38 expression on lymphoma samples by liposomal ATRA. One of skill in the art would under stand that the increased level of CD38 would improve the efficacy of the 3BIT combination of Flavell et al and would also increase the efficacy of the CD38-saporin immunotoxin used as a single immunotoxin versus the cocktail of immunotoxin because increasing the level of CD38 on the cell surface would provide more chance for any given lymphoma cell to internalize a anti-CD38 immunotoxin.

7. Claims 1, 5, 7, 8 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldmacher et al (Blood, 1994, Vol. 84, pp. 3017-3025) in view of Schlom ('Monoclonal AntibodiesThey'reMore and Less Than You Think', In: Molecular Foundations of Oncology, 1993, S. Broder, Ed, pp. 95-134) and Drach (Cancer Research, 1994, Vol. 54, pp. 1746-1752).

Claim 1 is drawn in part to a method of treating an individual having lymphoma comprising administering to said individual a pharmacologically effective dose of a retinoid which up-regulates the expression of CD38 antigen and administering to said individual a pharmacologically effective dose of an immunotoxin directed against the up-regulated CD38 antigen. Claim 15 embodies the method of claim 1 wherein said pathophysiological state comprises myeloma.

Goldmacher et al teach a method of exerting selective cytotoxicity on myeloma cells ex vivo comprising contacting said cells with an anti CD38 immunotoxin comprising ricin (pages 3021-3022, under the heading of "Effect of HB7-blocked ricin on multiple myeloma cells isolated from patients"). Goldmacher et al suggest, based on the action of an anti-B4 blocked ricin, that the administration of the CD38 immunotoxin to patients, including patients having multiple myeloma, would be expected to be tolerable (page 3023, second column, lines 8-21). Goldmacher et al does not teach the administration of an antiCD38 immunotoxin comprising gelonin, or the administration of the antiCD38 immunotoxin with ATRA.

Schlom teaches that it is well known in the art that virtually any component of a tumor cell is susceptible to modulation. Schlom teaches that the practice of receptor modulation to increase the level of extracellular receptors targeted by monoclonal antibodies (pages 109-110 under the heading of "Up Regulation of Target Antigens") is recognized in the art.

Drach et al teach that CD38 expression is includible in myeloid cells via the retinoid acid receptor alpha (pages 1747-1748, under the heading of "Expression of CD38 in Differentiated HL-60 and KG-1 Cells").

It would have been prima facie obvious at the time the claimed invention was made to administer the anti-CD38 immunotoxin comprising ricin to patients having multiple myeloma. It would have also been prima facie obvious to administer an antiCD38 immunotoxin comprising gelonin. One of skill in the art would have been motivated to do so by the teachings of Schlom on the well known principle of receptor modulation to increase the level of a target receptor on the cell surface, and the teachings of Drach et al on the modulation of the CD38 antigen in myeloid cells via ATRA and the retinoic acid receptor alpha. One of skill in the art would expect that the ATRA would increase the level of the CD38 target antigen on the multiple myeloma cells to insure that more binding of the anti-CD38 antibody.

8. Claims 1, 7-9, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta et al (Proceed Amer Assoc Cancer Res, 1997, Vol. 38, page 88, cited in a previous Office action) in view of O'Connor et al (Blood, Vol. 86, pp. 4286-4294).

Claim 1 is drawn in part to a method of treating an individual having drug resistant leukemia comprising administering to said individual a pharmacologically effective dose of a

retinoid which up-regulates the expression of CD38 antigen and administering to said individual a pharmacologically effective dose of an immunotoxin directed against the up-regulated CD38 antigen. Claim 9 embodies the method of claim 8, wherein said toxin is gelonin. Claim 12 embodies the method of claim 1 wherein said pathophysiological state comprises drug-resistant leukemia. Claim 13 embodies the method of claim 12 wherein the drug-resistant leukemia is adriamycin-resistant leukemia.

Mehta et al teach that retinoic acid increases the expression of CD38 on leukemia cells ex vivo and leukemia cell lines. Mehta et al teach that retinoic acid treatment of leukemia cell lines increase the toxicity of an anti-CD38 gelonin immunotoxin. Mehta et al do not teach the actual administration of anti-CD38 gelonin immunotoxin to patients with leukemia or drug resistant leukemia.

O'Connor et al teach that drug resistance in tumors can be overcome by treating with agents which have different mechanisms of action which are still effective in the drug resistant tumor cells. O'Connor et al suggest that an immunotoxin binding to a receptor followed by internalization and delivery of the toxic portion to inactivate ribosomes in the cytoplasm is not a toxic mechanism common to chemotherapeutic drugs current in use (page 4286, second column, lines 3-14).

It would have been prima facie obvious at the time the claimed invention was made to administer the anti-CD38 gelonin immunotoxin in combination with retinoic acid to patients having drug resistant leukemia or adriamycin-resistant leukemia. One of skill in the art would have been motivated to do so by the teachings of O'Connor on the efficacy of providing an immunotoxin which exerts toxicity through internalization and inactivation of ribosomes in the cytoplasm. One of skill in the art would expect that the retinoic acid would increase the likelihood of a immunotoxin molecule to bind to a target cell because the target cell would express more CD38 due to treatment with the retinoic acid. One of skill in the art would expect that an individual having leukemia cells which were resistant to adriamycin would be sensitive to an immunotoxin comprising gelonin because O'Connor et al teach that ribosomal toxicity is not common to the chemotherapeutic drugs in current use which include adriamycin.

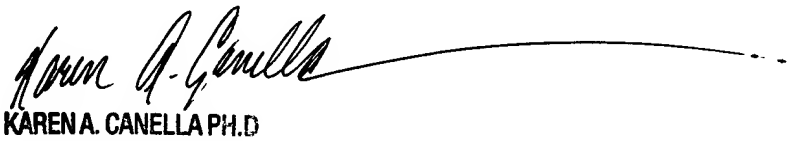
9. All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
3/6/2006



KAREN A. CANELLA PH.D
PRIMARY EXAMINER